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The purpose of these investigations is to determine whether symptoms of acute mountain sickness (AMS) are affected by mensrual cycle phase and oral contraceptives in women and whether the severity of AMS differs from men. The experimental test procedures have been selected, tested and performed on 10 subjects. The experiments consist of 12-hour exposures to a simulated altitude of 16,000 ft. Measurements of global and regional (brain magnetic resonance imaging) fluid homeostasis, ventilation, cognitive and autonomic function are emphasized in relation to control measurements and AMS symptoms. Women are tested in luteal and follicular phases of the menstrual cycle, confirmed by progesterone levels, and while on contraceptives and compared with men. Early results (n=10) suggest that a constant urine volume and transcapillary albumin escape rate and a declining plasma volume at altitude are associated with a high tolerance to AMS.

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Jack Loyly 28 Oct 197

PI - Signature Date

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INTRODUCTION

This is the first annual report of the study entitled "The Physiology of Acute Mountain Sickness in Women." It describes the established methods and those results which are available to date. An abstract, essentially as submitted with the initial contract application in November of 1995, describes the overall objectives:

"Women are becoming more prevalent as military personnel, but we lack basic knowledge about their physical and mental performance at high altitude. Military personnel deployed to high altitudes will be exposed to the hazards of hypobaric hypoxia and a significant number are at risk to develop acute mountain sickness (AMS). The deleterious impact of AMS on military operations has been demonstrated in both experimental studies and actual conflict. However, very few laboratory or field studies have examined AMS in women. Also, no laboratory studies have compared the responses of women and men exposed to high altitude. Thus, as more women are included in a wider variety of Army units, AMS can potentially result in a significant loss of unit strength and could jeopardize the accomplishment of a unit's mission. We are planning to study the effects of the menstrual cycle and oral contraceptive use in women on AMS and compare the results with men. The measurements for comparison will focus on fluid balance and distribution, including brain scans for cerebral edema, ventilatory and circulatory responses, autonomic nervous system function and cognitive function. In the past two years, in related studies, we have collected important data that began to address each specific aim and established that we are capable of the careful execution and analyses of the proposed study. This study will make a major contribution to the understanding of the requirements of female soldiers and other military personnel who may be exposed to high altitude."

The research performed to date may seem somewhat inadequate, considering the planned number of subjects to be tested in the 3-year span of the contract. To date the data collection is about 12% of the total proposed. The reasons for this apparently slow start are many and constitute the majority of the work done the first year: a) resolving the final test procedures to be employed and obtaining the required equipment and supplies and pretesting these in pilot studies, b) finalizing and streamlining procedures and logistics required for this particular study, because they deviate from studies we have done in the past, c) upgrading the altitude chamber facility, d) hiring personnel and training them to perform the necessary tasks, e) obtaining IRB approval for the many test procedures from a number of organizations, f) working out arrangements for the various subcontracts and g) streamlining the methods of obtaining volunteers and selecting subjects. We are now in a position where the experiments

are running smoothly and the pace of data collection is increasing in order to accomplish the proposed tasks in the time frame originally stated.

BODY

A. Experimental Methods and Procedures:

In order to give a realistic overview of the experimental logistics, test procedures and methods as they are now established and performed, we summarize below the general instructions for the study as we present them to potential subjects during our initial contact with them:

Logistics: You will meet with certain members of the scientific staff a number of times before the altitude experiments to receive information, a medical examination and to practice laboratory tests. These tests have been finalized as a result of preliminary testing by the scientific team on themselves to optimize the protocols. You will eventually be scheduled for a 2-day block of experiments. Prior to this 2-day block you will make at least three more visits to this facility.

Men will complete one 2-day block. Women will complete two 2-day blocks, one in the follicular and one in the luteal phase, and perhaps a third when you are on oral contraceptives. Details of how we will determine these menstrual phases will be described to you.

All tests will take place at the altitude chamber laboratory. For the 2-day protocol, on the first day (Control day) you will report to the altitude chamber laboratory, where you are now. You will report to the chamber at 1:00 PM for certain measurements, after having followed specific instructions, regarding your fluid intake and eating, and remain with us for the rest of the day, doing various test procedures, followed by the magnetic resonance imaging (MRI) exam at the nearby VA Medical Center. After this you will go home and then report to the altitude chamber early the next morning. This day (Chamber day) you will spend at an altitude equivalent to 16,000 feet (barometric pressure = 426 mm Hg) in the chamber. After 12 hours in the chamber (or less if your symptoms of altitude sickness are unusually severe), you will be transported to the VA Medical center for another MRI. During this time of transport from chamber to MRI you will be breathing a gas mixture through a face mask that keeps your lung and blood oxygen level approximately what it was in the chamber (13.5% oxygen). Below are summarized the main test procedures that will be performed.

Eating: Somewhat regulated for 3 days before the study, basically minimizing unusual deviations from your normal diet. The supplied food listed below will be obtained by a nutritionist, based on a detailed normal diet and eating record you will supply for us weeks before the study. Pre-Control day -supplied dinner, Control day (day before the altitude chamber day) -supplied breakfast, lunch, snack and dinner, Altitude chamber day -supplied breakfast, lunch and snack.

Water or fluid intake: Specific intake (slight overload which will increase frequency of urine voiding) on Control day with minimal variations allowed, based on individual requirements. Specific intake (slight overload) on Altitude chamber day with few options.

Cognitive tests: Logic, problem solving and reaction time tests taken on a keyboard at specific times. These will be practiced before the 2-day testing during the preliminary visits.

Symptom questionnaires: Questions about how you feel. These will also be practiced before the 2-day testing.

Blood pressure and Heart rate: Taken periodically with automatic arm cuff and also recorded by ECG.

Spirometry: Breathing tests done at specific times to measure vital capacity and how fast you can exhale on a single breath.

Breathing measurements: Periodically made to measure the rate and depth of resting breathing. Measured by breathing through a tube with mouthpiece attached. This will also be practiced.

Fluid Balance: The amount of fluid you drink and the amount of urine you eliminate will be measured at precise times throughout both days. Other fluid compartments will be measured as listed below:

Deuterium oxide- this is a naturally occurring isotope of water. You will drink 10 mls of this at a specific time once on each of the two days. It is cleared from your body over time by your natural body water turnover. Periodic blood samples taken and measured allow us to determine your total body water.

Sodium Bromide- this is a salt solution (NaBr) You will drink 2 grams of this, which is dissolved in the deuterium oxide and regular water, at a specific time once on each of the two days. This substance is also cleared from your body by electrolyte turnover. Blood samples allow us to determine your extracellular water.

Evans blue dye- this is a dye which attaches to the albumin in your blood plasma. You will receive one injection of 12 milligrams into an arm vein at a specific time on each of the two days. It is removed from your body by your liver in about 36 hours. The dye concentration in your blood allows us to measure your plasma volume.

Venous blood: Numerous substances will be measured in your blood. Before the control day this blood will be obtained from a single "stick" in your arm on one or more days to obtain your hormone levels and for blood screening purposes. On the control day a catheter will be inserted into an arm vein because a number of samples are required. On the chamber day the catheter will be inserted in your arm in the morning and left in all day to provide a convenient and painless method to obtain the numerous samples required throughout the 12-hour altitude exposure.

Arterial blood: On the control day one arterial sample will be obtained in the late afternoon. On the chamber day two arterial blood samples will be obtained from you, one early during the exposure and one near the end. Each time, a needle will be inserted into a femoral (leg), brachial (upper forearm) or radial (wrist) artery by a physician. This will be done after a local anesthetic agent is given at the chosen site. The sampling needle will remain in place only long enough to obtain the blood sample.

MRI (Magnetic Resonance Imaging): In this test you will be lying quietly on your back inside of a whole-body magnet. A magnetic field will be supplied to your body and this allows images to be obtained of your head. We wish to see whether altitude exposure will result in changes in the water content of certain head structures and thereby contribute to particular symptoms of acute mountain sickness.

Other tests: Prior to the altitude exposure day, other tests will be done. Some are repeated for practice to allow you to respond in a "natural " fashion later. Results of these tests may correlate with how well you do at altitude. Most of these tests will be done on the days preceding the Control day during your preliminary visits. These tests are the following: a) maximum exercise test on a bicycle, b) cold pressor test - measuring your heart rate and blood

pressure in response to placing your hand in ice water for 5 minutes, c) ventilatory response tests to hypoxia and carbon dioxide - you will breathe on a system that gradually lowers your lung and blood oxygen or raises your lung and blood carbon dioxide over a period of 5 to 10 minutes and we measure how much your breathing increases in response to these stimuli, d) altitude symptom scores, e) cognitive (mental) tests and f) personality or "mood" status questionnaire.

More specifically, the exact variables obtained and the times that the measurements are made are presented below. Appendix 1 is a detailed chronological list of the measurements as they are taken, used as our working guide.

Abbreviations:

ECW: extracellular water

PV: plasma volume

TBW: total body water

D_2O: deuterium oxide

GFR: glomerular filtration rate

TCER: transcapillary escape rate

LL: Lake Louise AMS symptom questionnaire

ESQ: environmental symptoms questionnaire

VA: visual analog test of symptoms

elect: Na+, K+

6 hormones: epi, norepi, aldo, ANP, ADH, PRA

PD: plasma density

PP: total plasma protein

CPT: cold pressor test

HVR: hypoxic ventilatory response test (poikilocapnic and isocapnic)

HCVR: hypercapnic ventilatory response test

General

These measurements assume that the exposure on the chamber day to 426 mm Hg (=16,000 ft, according to West (1)) will be for exactly 12 hours. In the event that the decision is made to curtail a run, because of intolerable AMS or for other reasons, the measurements or procedures scheduled for 4:00 PM will be started immediately and NaBr and D_2O samples will be collected before, or after leaving the chamber if necessary, at appropriate times. This schedule assumes that 3 hrs are required for the ECW-NaBr test (one sample after 3 hrs) and 3 hrs are required for TBW-D_2O (one sample after 3 hrs) and that 30 min minimum are needed

for the PV-Evans blue test (3 samples at 10 min intervals) and that TCER-Evans can be obtained from a 3 hr slope of Evans (3 early samples and additional samples after 1, 2 and 3 hrs). Water intake will equal urine output beginning at time zero and matched every 3 hrs. GFR will be estimated from creatinine clearance. Respiratory measurements include V_E, end-tidal O_2 and CO_2, VO_2, VCO_2 and R and arterial samples include P_aCO_2, P_aO_2, S_aO_2, pH and Hb. Arterial samples will be obtained from a single needle stick at the 2 times indicated (and once on the control day).

One Month or more before experiments (Women)

Menstrual cycles are determined by a combination of interview, dates of menses and daily recording of oral temperature (taken in the morning). When this is determined and the subject is tentatively scheduled one or more months in advance, the projected date of the LH surge is confirmed with an LH kit by the subject. The time period of elevated progesterone in the luteal phase is usually determined in the cycle before the one in which experiments are done by blood progesterone assays. The 4th day following the LH surge will probably be the day the control day testing (preceding the chamber day) will be scheduled on the next cycle, depending on subject's cycle history and other blood progesterone fluctuations measured periodically in weeks preceding actual experiments.

Second, Third and Fourth Subject Visits (the 4th visit should be at least one week before the chamber day)

-Turn in consent form, blood sample taken for screening, iron and iron binding

-History and physical exam

-Subject brings 3-day food record

-Give out LH kits and instructions, if female

-Practice cognitive tests at least 8 times during visits 2, 3 and 4. A total of 8 practice runs must be performed before the control day

-Maximum exercise test. Borg and pain scale are given during test

-Practice ventilatory response tests. Practice poik, iso and HCVR. These are to be given on control day in order of: HVRpoik (twice) HVRiso, HCVR, 3 breaths N_2 (twice) and 3 breaths O_2 (once).

Two days before control day

Subject maintains average daily lifestyle and eats normally. The Na+, K+, calories, fat, protein and carbohydrate as given for diet records. These are matched by the food given the subject on the control and altitude day.

TIME OF MEASUREMENTS

Day 1: Control day, Day 2: Altitude day

Food: Day 1: 6:30 AM, 11:00 AM, 3:30 PM, 9:00 PM

Day 2: 5:30 AM, 11:00 AM, 3:30 PM

Weight: Day 1: 1:00 PM, 4:00 PM, 7:00 PM

Day 2: 7:00 AM, 10:00, 1:00 PM, 4:00 PM, 7:00 PM

Body Temp: Day 1: 7:00 PM

Day 2: 7:00 AM, 1:30 PM, 7:00 PM

HVR and HCVR: on control day afternoon

3-breath tests: on control day afternoon and after 1, 6, and 12 hr in chamber

Maximal Exercise: twice before control day

Cold pressor test: on control day afternoon

Respiratory (metabolic)

Day 1:	Day 2:
6:30 PM + arterial blood	8:30 AM (1) + arterial blood
	1:30PM (6)
	6:30 PM (12) + arterial blood

Symptoms (LL+VA's)

Day 1:	Day 2:
2:30 PM (practice)	6:30 AM (0)
6:00 PM add ESQ	8:00 AM (1) add ESQ
	1:00 PM (6) add ESQ
	6:00 PM (12) add ESQ
	8:30 PM, Post MRI

Heart rate & blood pressure

Day 1:	Day 2:
6:30 PM	8:30 AM (1)
	1:30 PM (6)
	6:30 PM (12)

Cognitive testing

Day 1:	Day 2:
2:00 PM (practice)	8:30 AM (1)
6:30 PM	1:30 PM (6)

6:30 PM (12)

Spirometry

Day 1:	Day 2:
6:30 PM	8:30 AM (1)
	1:30 PM (6)
	6:30 PM (12)

Fluids:

1) TBW (D_2O) Day 1: Drink 4:00 PM - sample 6:00 and 7:00 PM
Day 2: Drink 4:00 PM - sample 6:00 and 7:00 PM

(2) ECW (NaBr) Day 1: Drink 4:00 PM - sample 6:00 and 7:00 PM
Day 2: Drink 4:00 PM - sample 6:00 and 7:00 PM

(3) Plasma Volume (Evans) Day 1: Inject 4:00 PM- sample 4:10 PM, 4:20 PM, 4:30 PM
Day 2: Inject 4:00 PM- sample 4:10 PM, 4:20 PM, 4:30 PM

(4) TCER (Evans) Day 1: Inject 4:00 PM- sample as above plus 5:00, 6:00 PM, 7:00 PM
Day 2: Inject 4:00 PM- sample as above plus 5:00, 6:00 PM, 7:00 PM

(5) Urine (volume):

Day 1:	Day 2:
6:00 AM and balance	5:00 AM and balance
4:00 PM and drink	7:00 AM and drink (0)
7:00 PM (collect), ad lib	10:00 AM (collect, 0-3) and drink
	1:00 PM (collect, 3-6) and drink
	4:00 PM (collect, 6-9) and drink
	7:00 PM (collect, 9-12) and ad lib
	8:30 PM post MRI, (collect)

Albuminuria, urine elect, osmol and creatinine for GFR

Day 1:	Day 2:
7:00 PM	10:00 AM (1)
	1:00 PM (6)
	4:00 PM (9)
	7:00 PM (12)
	8:30 PM (post MRI)

Venous blood: creat (for GFR), elect, PP, osmol, PD, Hct, 6 hormones, extra plasma

Day 1:	Day 2:

6:00 PM	8:30 AM (1)
	1:00 PM (6)
	6:00 PM (12)

Venous blood: progesterone Day 1: 7:00 AM Day 2: 6:00 AM

Venous blood: Epi, Norepi Day 1: taken before and during last min of CPT.

The basic assumption for this study is that as subjects develop AMS symptoms, the progressive severity will correlate with many of the variables measured during the course of the altitude exposure, thus helping to explain the pathophysiology. The exercise, autonomic and ventilatory measurements taken before the chamber exposure may serve similar purposes and will also be substantiated regarding their validity in predicting AMS for individuals, menstrual cycles and oral contraceptives.

B. Results and Discussion

We present here the data collected and analyzed to date. Some of the analyses will be performed by other laboratories and are not yet available because these are best run in batch. (Catecholamines by Dr. Kamimori at Walter Reed and aldosterone, atrial natriuretic peptide, antidiuretic hormone and plasma renin by Dr. Hinghofer-Szalkay at the University of Graz, Austria). To date we have performed 10 complete experiments. These include 5 male subjects, 2 females in both menstrual phases and another female in the follicular phase. We currently have seven eumenorrheic women and 5 men waiting to be tested, who have all completed pretesting. Six more women and six men are in various stages of pretesting.

Symptom Scores: Table 1 shows the Lake Louise Symptom Scores obtained on the subjects. These show the expected variations among individuals. A ranking of the subjects based on mean AMS score has been made. Based on the minimum criterion of a score of 2, with a headache of 1, as indicating the presence of AMS (2), 8 of the subjects had AMS and subject F-2(L) and M-4 did not. The five women's average scores tended to be lower ($P<0.10$) than the male's (1.5 vs. 3.3). It is notable that significant AMS was still present in 6 subjects after the MRI scan, some 1.5 hours after the subjects had been in a normal oxygen environment. In the two women studied in each menstrual phase there was a tendency for the AMS to be lower in the luteal phase.

Table 1. Age, serum progesterone (ng/ml) and Lake Louise symptom scores 12 hr before (C12), at 1, 6, and 12 hr (A1, A6, A12) and 1.5 - 2 hr after altitude exposure (post).

SUBJ	AGE	PROG	C12 †	A1 †	A6 †	A12 †	POST †	MEAN*	RANK
F-1(F)	25	0.3	2(0)	1(1)	3(1)	1(1)	1(0)	1.7	6
F-1(L)	-	12.8	0(0)	1(0)	3(1)	1(1)	1(0)	1.7	7
F-2(F)	32	0.3	0(0)	0(0)	2(0)	3(1)	2(2)	1.7	5
F-2(L)	-	10.9	1(0)	1(0)	1(0)	1(0)	2(1)	1	9
F-3(F)	27	0.4	0(0)	0(0)	1(1)	3(2)	3(3)	1.3	8
M-1	32	-	1(0)	3(0)	5(1)	6(2)	6(2)	4.7	3
M-2	23	-	2(1)	0(0)	6(0)	9(3)	10(3)	5	1
M-3	26	-	1(0)	4(1)	3(1)	8(3)	8(3)	5	2
M-4	25	-	0(0)	0(0)	0(0)	0(0)	0(0)	0	10
M-5	30	-	0(0)	0(0)	2(1)	3(2)	1(1)	2	4

* Mean from three values at altitude.

† Scores are totals, with headache score in parentheses

Ventilation: The ventilation is shown in Table 2. The subjects increased ventilation about 24% during the three altitude measurements in relation to normoxia baseline. The percentage increase was not correlated significantly with AMS score ($r = -0.03$). The percent increase in ventilation at simulated altitude was greater for males than females ($P<0.05$) and there was no consistent difference with menstrual cycle in the two females studied. The acute hypoxic ventilatory sensitivity , as measured with the 3-breath nitrogen test and shown in Table 3, did not show any clear difference within subjects during the 12 hours at altitude or between the altitude tests and the baseline tests the day before in normoxia. This measurement also did not correlate significantly with AMS score ($r = -0.23$). The average score between men and women was about the same and menstrual phase did not alter the value between the two women.

Arterial blood gases: These results are shown in Table 4. The arterial blood pH increased significantly from the 2nd to the 12th hour at altitude by an average of 0.027 pH units. The PCO_2 fell by 4 mm Hg, although the ventilation remained about the same. The calculated increase in base excess (3) is approximately 1.0 mEq/L over the 10 hours, indicating the elimination of bicarbonate by the kidneys over this relatively short time at altitude. The arterial PO_2 increased by 3 mm Hg on the average and increased the arterial O_2 saturation from 83 to 84%. Table 4 also shows the change in the end-tidal (alveolar) - to - arterial PO_2 difference measured during the 2nd and 12th hour. The mean difference was reduced by about 1 mm Hg, indicating that gas exchange efficiency may have improved and that there was no greater diffusion impairment or shunt at A12 than at A1. The arterial - alveolar PCO_2 also declined during the altitude exposure, diminishing by 3 mm Hg. This demonstrates a general absence of any increase in ventilation/ perfusion mismatch over time at altitude. There was no correlation between these alveolar - arterial differences and AMS symptom scores. The blood gas values also did not show a relationship with AMS scores. No appreciable differences were seen between males and females or between menstrual cycles.

Body water: The analyses for the completed runs have not all been performed because the analyses are done at another commercial laboratory. From the values shown in Table 5, it is apparent that the A12 values for extracellular water (ECW) are, on the average, unchanged from the preceding control day. An increase in ECW would be supportive of generalized edema, which would be anticipated to be directly related to AMS symptoms. The values for total body water (TBW) show small changes, averaging 3% less at altitude. The difference between these two measures is intracellular water (ICW), which gave an average

Table 2. Ventilation (L/min) 12 hr before (C12) and after 1, 6, and 12 hr (A1, A6, A12) of altitude exposure .

SUBJ	C12	A1	A6	A12	Δ %
F-1(F)	10	7.8	6.1	6.5	-32
F-1(L)	6.7	9.3	9.1	7.8	30
F-2(F)	9.2	12	12.9	12.1	34
F-2(L)	10.5	10	7.9	9.3	-13
F-3(F)	7.1	7.6	6.7	8.7	7
M-1	5.1	-	8.1	9.9	65
M-2	8.2	10.4	10.6	10.7	29
M-3	10.5	13.7	11.6	10.4	13
M-4	8	14.3	16.1	17.6	101
M-5	7.4	11.1	11.5	9.3	45
MEAN*	8.3	10.7	10.1	10.2	

Δ% : Percent change at altitude vs. C12

Table 3. Acute ventilatory response to 3 breaths of 100% N2 12 hr before (C12) and after 1, 6, and 12 hr (A1, A6, A12) of altitude exposure .

SUBJ	C12	A1	A6	A12	MEAN*
F-1(F)	7	5	5	12	7
F-1(L)	17	-5	-12	22	6
F-2(F)	86	58	73	33	63
F-2(L)	45	50	57	68	55
F-3(F)	35	6	61	-	34
M-1	31	-	75	33	46
M-2	-3	32	15	42	22
M-3	3	-	-	38	21
M-4	43	40	30	65	45
M-5	23	39	22	25	27

* Mean ventilatory response for each subject.
Values are percent increase in ventilation (measured for 35 sec) following N2 onset.

Table 4. Arterial blood gas values during the 2nd and 12th hr (A1, A12) at altitude.

	A1			A12				
SUBJECT	PO_2	PCO_2	pH	PO_2	PCO_2	pH	Δ PO_2	Δ PCO_2
F-1(F)	44	35.5	7.43	48.5	30	7.47	-6.4	-8.2
F-1(L)	45	30	7.43	49	25	7.45	0.1	-2
F-2(F)	50	36	7.44	50.5	31.5	7.465	1.6	-2.9
F-2(L)	43	29	7.44	47.5	26	7.465	-1.8	-1.2
F-3(F)	52	31	7.465	63.5	25	7.495	-3.7	-1.7
M-1				47.5	26	7.52		
M-2	49	31.5	7.415	47.5	29.5	7.435	1.6	1
M-3	48.4	36.1	7.45	52.7	28.3	7.496	-5.2	-6.9
M-4	51.3	32	7.42	52.5	30	7.44	3.1	-1.8
M-5	47	36.5	7.435	42.5	33.5	7.45	3.2	-2.2
MEAN	47	33	7.442	50	29	7.469	-1	-3

Δ PO2: End-tidal minus arterial PO_2 difference

Δ PCO2: Arterial minus end-tidal PCO_2 difference

Table 5. (a) Extracellular water (L) and (b) total body water (L) on control day and during last 3 hr at altitude.

(a)

SUBJECT	C12	A12	Δ % *
F-1(F)	9.3	10.1	8
F-1(L)	-	-	-
F-2(F)	14.6	14.6	-1
F-2(L)	14.0	13.3	-5
F-3(F)	10.0	11.7	17
M-1	17.4	16.6	-5
M-2	18.6	-	-
M-3	16.2	15.8	-2
M-4	18.6	18.3	-1
M-5	15.5	13.8	-11

(b)

SUBJECT	C12	A12	Δ % *
F-1(F)	25	24.2	-3
F-1(L)	-	-	-
F-2(F)	37.6	35.8	-5
F-2(L)	36.6	38.4	5
F-3(F)	27.6	28.2	2
M-1	46	44.5	-3
M-2	51.6	-	-
M-3	51.1	45.8	-10
M-4	50.5	46.9	-7
M-5	44.2	44.7	1

decline of 4%. These limited data show no clear differences related to gender or menstrual phases.

Urine Volume: All subjects reduced their urine volume during exposure to altitude, by 140 ml/hr or 37%, when comparing the values from the first half of the exposure with those from the second half (Table 6). When comparing A12 with C12, a significant correlation was noted between the urine volume decline and AMS symptom scores ($r = -0.74$, $P<0.02$). The two subjects who did not have AMS increased their urine volume at A12 relative to the control value.

Urine albumin: Albuminuria has been reported in longer exposures to real altitude and has been associated with AMS (4). Our measurements show, in general, that albumin increased with time at altitude. However, the correlation with AMS and differences between men and women are not yet apparent from the values shown. Interestingly, one of the women and two of the men demonstrated a transient rise in urine albumin at 6 - 9 hours, coinciding with the increase in their AMS scores. Most subjects had detectable albumin (above 200 micrograms/dL) in their urine collected 1-2 hours after the altitude exposure.

Plasma volume: The plasma volume (PV) values, measured with Evans blue dye, are shown in table 7. These values were obtained from zero-time extrapolation of a 3-hr decay curve of dye injected at the same time of day on the control day and after 9 hours at altitude. Samples were taken at 10, 20, 30, 60, 120, and 180 minutes after injection of 12 mg of dye. On the average the PV was 3% lower at altitude than during C12. It showed the greatest decline in the two subjects, F-2(L) and M-4, who did not have AMS. In fact, the percentage decrease in PV was highly correlated with the AMS scores (Table 1) with an $r = 0.80$, ($P< 0.01$).

Transcapillary escape rate (TCER): These values are also shown in Table 7, as determined from the decay slope of the dye, determined over 3 hours. The values are expressed as the percentage change in dye concentration per hour, which is representative of the rate of albumin loss from the vascular space per hour. Overall, the TCER was greater at altitude than on the corresponding control day. The change in TCER at altitude was related significantly ($P<0.05$) with the AMS scores ($r = -0.69$). This suggests that TCER is increased in subjects who develop AMS.

Magnetic Resonance Imaging (MRI) data collection and analyses: Every subject has undergone MRI at the end of the control day and at the end of the altitude chamber day. The MRI data collected include a) T1 weighted 3-D dataset, b) T2 weighted series of image slices

Table 6. (a) urine volume (ml/hr) and (b) urine albumin (μ/dl) 12 hr before (C12), after 1, 6, and 12 hr (A1, A6, A12) during, and 1.5 - 2 hr after altitude exposure (post).

(a)

SUBJECT	C12	A3	A6	A9	A12	POST
F-1(F)	110	201	33	49	23	47
F-1(L)	203	163	83	8	140	20
F-2(F)	564	393	415	336	369	-
F-2(L)	471	431	697	361	558	67
F-3(F)	341	621	601	293	415	90
M-1	893	628	114	215	147	233
M-2	647	382	65	57	200	167
M-3	-	-	303	370	380	97
M-4	227	443	644	167	293	400
M-5	151	387	491	259	293	60
MEAN	**383**	**395**	**351**	**213**	**254**	**136**

(b)

SUBJECT	C12	A3	A6	A9	A12	POST
F-1(F)	ND	ND	3650	1060	372	ND
F-1(L)	ND	ND	416	4860	341	619
F-2(F)	ND	ND	ND	ND	ND	270
F-2(L)	ND	ND	ND	ND	ND	676
F-3(F)	204	ND	ND	ND	ND	310
M-1	500	ND	750	250	ND	750
M-2	ND	330	934	573	ND	287
M-3	ND	ND	ND	ND	ND	ND
M-4	ND	ND	ND	ND	ND	ND
M-5	234	ND	ND	ND	ND	639
MEAN	**94**	**33**	**575**	**674**	**71**	**355**

ND are nondetectable values (< 200 μ/dl)

Table 7. (a) Plasma volume (ml) and (b) transcapillary escape rate (%/hr) on control day and during last 3 hr at altitude.

(a)

SUBJECT	C12	A12	Δ %
F-1(F)	2138	2105	-1.5
F-1(L)	2147	1995	-7.1
F-2(F)	3553	3407	-4.1
F-2(L)	3478	2926	-15.9
F-3(F)	2525	2402	-4.9
M-1	3196	3401	6.4
M-2	3897	3947	1.3
M-3	3749	3827	2.1
M-4	5144	4582	-9.1
M-5	4214	4184	-0.7
MEAN	3404	3287	

(b)

SUBJECT	C12	A12	Δ %
F-1(F)	-9.4	-5.8	3.6
F-1(L)	-5.2	-6.4	-1.2
F-2(F)	-5.1	-4.9	0.3
F-2(L)	-5.9	-12.6	-6.6
F-3(F)	-5.1	-2.9	2.2
M-1	0.6	-9.1	-9.7
M-2	2.2	-3.9	-6.1
M-3	-4.9	-13.5	-8.6
M-4	-2.7	-1.3	1.4
M-5	-14.2	-8.3	5.9
MEAN	-5	-6.9	

through the cerebellum and cerebrum, c) Magnetization Transfer Contrast (MTC) slice series and d) Diffusion weighted slice series.

The T1 weighted 3-D data set is used to orient the slice selection so that the slices match on the control and post altitude days. This data set is also being analyzed to evaluate the brain for any changes in tissue volume. As demonstrated in the attached images from subject M-2 (Fig. 1: images a - d), 2-D images from the 3-D set are manually segmented into the cerebellum, brainstem above the first cervical vertebrae and cerebellum. Using a consistent signal threshold in each pixel, the pixels are identified as tissue or non-tissue for each region. The tissue volume is calculated by counting the pixels from all of the 2-D images in the 3-D dataset from each segmented region of the brain. The parts of the analysis that are operator-dependent have the operator blinded to which part of the protocol the images came from.

The T2 weighted, MTC and Diffusion weighted images are placed and oriented in the same region of the brain for each study by localizing the slices using landmarks from the 3-D T1 dataset. This allows subtraction of these images for data analysis as shown in Fig. 2. This figure depicts T2 images from subject M-3, whereby the image obtained after altitude exposure (Post) has been subtracted from the control image the day before (Pre) to give the "Post minus Pre" image. Due to minor localization differences, brain pulsatility, and subject motion, the image margins are of limited use. However, as little as a 3 to 5% signal difference in larger tissue regions is quite evident after image subtraction.

Other results: Data pertaining to diet during the control and altitude day are also compiled from analyses of diet records. Specifically, amounts of carbohydrates, fats, protein, calories, sodium and potassium are obtained. The fluid intakes are available to be tabulated to compute fluid balance, once a sizable number of subjects have been studied.

From the "correlative" tests we have other values to characterize the subjects. These include the maximal exercise responses of ventilation, heart rate, oxygen uptake and perceived exertion, the hypoxic and CO_2 ventilatory sensitivity and heart rate, blood pressure, perceived pain and the catecholamine response to the cold pressor test.

The cognitive tests include the following seven tests as part of the Walter Reed Performance Assessment Battery (PAB) of tests utilized by the Army: a) Choice Reaction Time, b) Logical Reasoning, c) Delayed Recall, d) Code Substitution, e) Stroop, f) Stanford Sleepiness Scale and g) Profile of Mood States. The "AMS-C" score, as obtained from the Environmental Symptoms Questionnaire, is also computed and will be used in addition to the

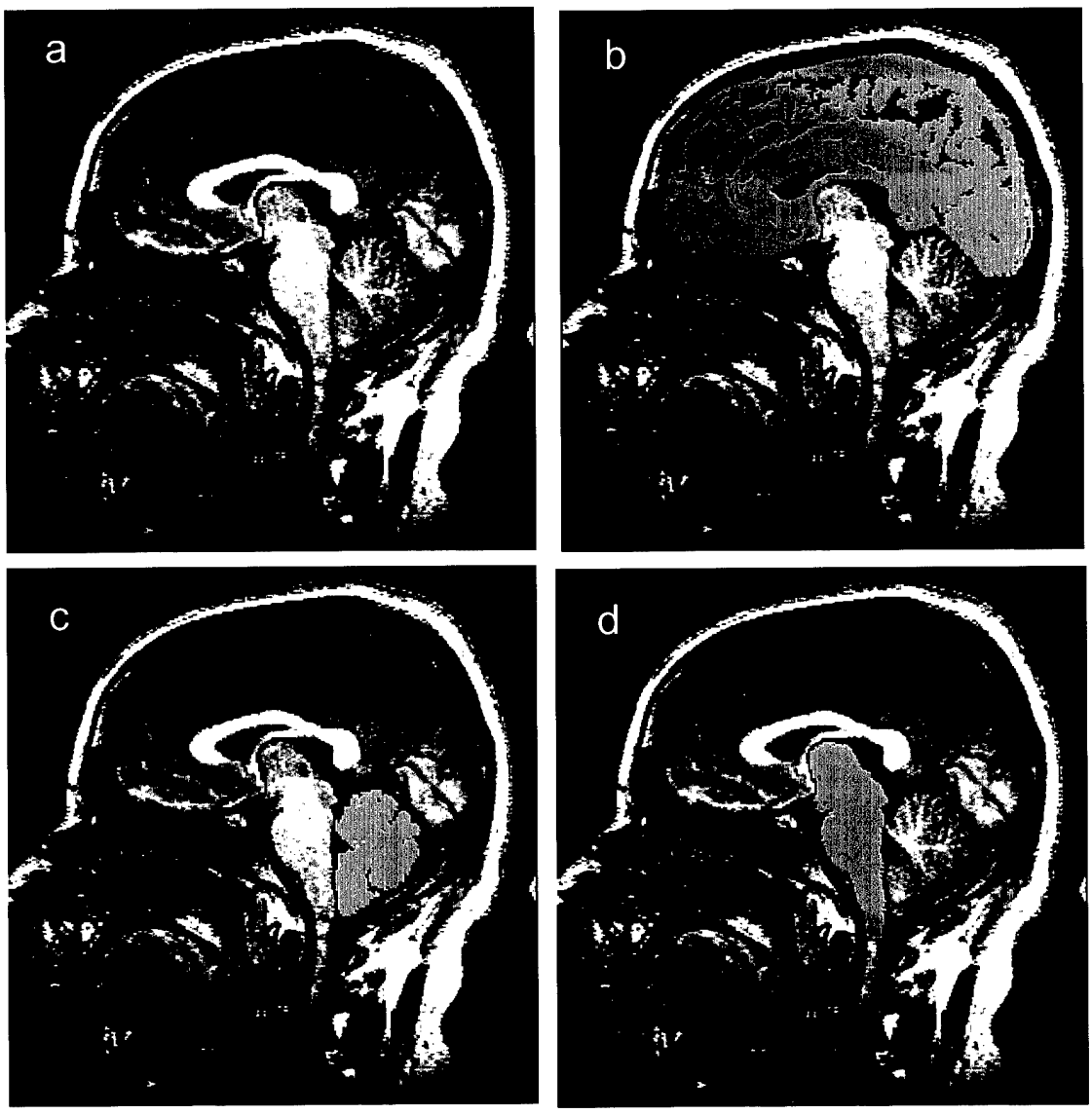

Figure 1: One slice from a T_1 weighted 3D data set with the cerebellum, brainstem and cerebrum segmented manually (purple line, Fig. 1a). The pixels identified as tissue are labeled with blue for the cerebrum (b), the cerebellum (c), and the brain stem (d).

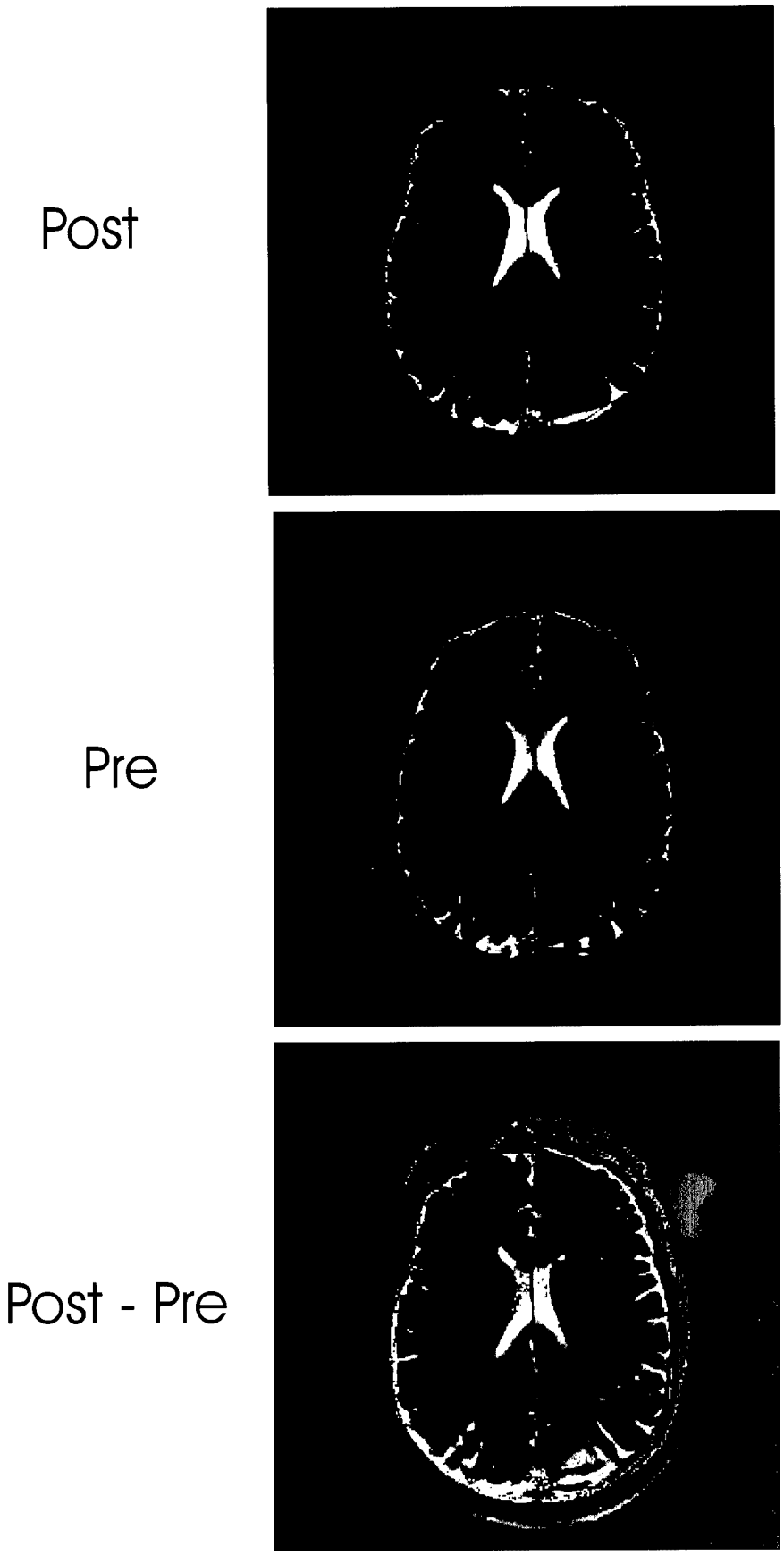

Figure 2.

Lake Louise AMS scores to determine AMS severity. These are all compiled on appropriate software while they are given on the control day and three times during altitude exposure after 1,6, and 12 hour.

Various other indices related to fluid homeostasis, in addition to the directly measured hormones, will be calculated from measurements being compiled. These include: sodium and potassium excretion and clearance, glomerular filtration rate, free water clearance from plasma and urine osmolality measurements and total blood volume. Most of these measures of fluid balance and regulation will be available serially during the exposure from analyses of the venous blood and urine samples.

All data is being compiled and stores on an EXCEL template. We have essentially completed the formatting of data storage and it will be accumulating as subsequent tests are completed.

C. Recommendations to Statement of Work

The objectives of the original statement of work remain unchanged, i.e., to determine whether symptoms of AMS are altered by a) menstrual cycle phases and b) by oral contraceptives. We are on the schedule originally given to complete the experiments on the men. We will not be able to adhere to the original schedule calling for the completion of experiments on 18 women in both menstrual phases in 16 months. In order to compensate for this delay in the long run, we will begin testing women on contraceptives concurrently instead of waiting until the third year. In this way we should be nearer the overall time table for the three-part study after the second year.

CONCLUSIONS

In five men and three women (two studied twice) we have observed the range of AMS scores expected when volunteers of this age range are randomly selected. Results pertaining to ventilation, blood gases, and diuresis were as anticipated based on previous studies. Provocative preliminary data suggest that a loss in plasma volume at altitude may be beneficial in deterring AMS and that an increase in transcapillary escape rate is detrimental. Any

generalized conclusions drawn from this few subjects is obviously premature in the overall context of the planned study.

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A paper by the current investigators, summarizing previous research findings pertaining to women at altitude, is given in Appendix 2.

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APPENDICES

Appendix 1(4 pages) and appendix 2 (6 pages) follow:

Appendix 1

WORKING GUIDELINE FOR EXPERIMENTAL TASKS AND PROCEDURES

DAY 1 (CONTROL)

"Morning Baseline"procedures

6:00 - 6:30 AM
1)Subject voids overnight urine and measures volume
2) Drinks water (and/or breakfast drink) to total 1,000 ml (or as adjusted for sleep time) when added to urine volume
3) Eats standard breakfast and drinks water or juice, etc., in addition, to total 0.5% of body weight. Can have one cup of coffee/tea, if usual, included in the above

Subject reports to the chamber laboratory at 1:00 PM and remains there for the rest of that day.

1:00 -3:00 PM
1) Record body weight and attach EKG electrodes
2) Insert venous cannula
3) Venous blood draw, (if female, progesterone only)
4) Practice Symptom scores (LL, VA's, ESQ)
5) Practice Cognitive tests twice
6) HVR (poik, poik, iso) and HCVR and 3-breath N_2 and O_2 tests
7) Cold pressor test: measure baseline BP, HR, epi and norepi. Then BP and HR and pain index every min for 5 min and draw sample for epi and norepi during the last min.

3:30-4:00
(1) Void Urine and drink to equal volume
(2) Eat snack
(3) Record weight
(4) Draw baseline for Evans, NaBr and D_2O

4:00
(5) Drink D_2O-NaBr cocktail, record exact time
(6) Inject Evans, record exact time (e.g. 4:00 PM)

4:10 Venous blood (Evans) , record exact time

4:20 Venous blood (Evans) , record exact time

4:30 Venous blood (Evans) , record exact time

5:00 Venous blood (Evans) , record exact time

5:00 - 6:00 Check stick-on electrodes. Then subject rests quietly, lights out, to be at basal state for subsequent hormone draw, calibrate and update Consentius metabolic device

6:00-7:00 PM **"Hour 12:00" Control measurements**
1)Venous blood (Evans, NaBr, D_2O, 6 hormones, extra plasma, elect, creat, PP, osmol, PD, Hct), record exact time
2) Spirometry
3) Symptoms (LL, VA's, ESQ)

4) Cognitive testing
5) Check "record" button on Consentius to record following resp. file
6) Anesthetic for arterial, calibrate and set end-tidals
7) Respiratory measurements (plus end-tidal, BP, HR)
8) Arterial Blood
9) "End test" on Cons. and save Cons. file to appropriate HRV directory and rename as "3-breath" for next test
10) 3-breath N_2 test (twice) and 3-breath O_2 (once), record end-tidal cals

(7:00) 11) Venous blood (Evans, NaBr, D_2O) , record exact time
12) Void urine, collect sample, (protein, elect, creat, osmol), and drink ad lib
13) Record weight
14) Record body temp

Remove catheter

(7:15-7:30) **Go to VAMC for baseline MRI**
Symptom scores (LL, VA's) after MRI
Prescribed evening meal after MRI

DAY 2 (ALTITUDE CHAMBER)

5:00 - 5:30 AM Subject arrives at chamber with overnight urine (if necessary)
1) Voids overnight urine (volume only)
2) Drinks water(and/or breakfast juice) if needed to total 1,000 ml with urine volume
3) Eats standard breakfast and drinks water or juice, in addition, to total 0.5% of body weight

5:30-6:30 4) Insert venous catheter
5) Venous blood draw, if female (progesterone only)

"Normoxia Baseline" measurements

6:30-6:45 1) Symptoms (LL+ VA's)
2) Void and drink

6:45-7:00 Enter chamber, ascent to 426 mm Hg (16,000 ft)
1) Set "Time zero" on clock
2) Record weight
3) Record body temp

7:30-8:00 Rest and lights out for subsequent hormones

"1 hr" measurements at altitude

8:00-9:00 AM 1) Venous blood (6 hormones, extra plasma, elect, creat, PP, osmol, PD, Hct)
2) Spirometry
3) Symptoms (LL, VA's, ESQ)
4) Cognitive testing
5) Check "record" button on Consentius to record following resp. file
6) Anesthetic for arterial, calibrate and set end-tidals
7) Respiratory measurements (plus end-tidal, BP, HR)

8) Arterial Blood
9) "End test" on Cons. and save Cons. file to appropriate HRV directory and rename as "3-breath" for next test
10) 3-breath N_2 test (twice) and 3-breath O_2 (once), record end-tidal cals
11) Record body temp

10:00 1) Void urine (0-3 hr interval) and collect (protein, elect, creat ,osmol) and drink
2) Record body weight

11:00 AM -12:00 Lunch Time
12:30-1:00 Rest and lights out for subsequent blood draw

"Hour 6" measurements at altitude

1:00-2:00 PM 1) Venous blood (6 hormones, extra plasma, elect, creat, PP, osmol, PD, Hct)
2) Void urine (3-6 hr interval) and collect (protein, elect, creat ,osmol) and drink
3) Record body weight
4) Spirometry
5) Symptoms (LL, VA's, ESQ)
6) Cognitive testing
7) Check "record" button on Consentius to record following resp. file
8) Respiratory measurements (plus end-tidal, BP, HR)
9) "End test" on Cons. and save Cons. file to appropriate HRV directory and rename as "3-breath" for next test
10) 3-breath N_2 test (twice) and 3-breath O_2 (once), record end-tidal cals
11) Record body temp

3:30-4:00 1) Void urine (6-9 hr interval)and collect (protein, elect, creat, osmol) and drink,
2) Snack time
3) Record body weight
4) Draw baseline blood for D2O, NaBr, Evans
5) Drink D_2O-NaBr cocktail, record exact time
4:00 6) Inject Evans, record exact time (e.g. 4:00 PM)
4:10 Venous blood (Evans) , record exact time
4:20 Venous blood (Evans) , record exact time
4:30 Venous blood (Evans) , record exact time
5:00 Venous blood (Evans) , record exact time
5:00 - 5:30 Check stick-on electrodes
5:30-6:00 Subject rests quietly, lights out, to be at basal state for subsequent blood draw, calibrate and update Consentius

6:00-7:00 **"Hour 12:00" Altitude measurements**
1) Venous blood (Evans, NaBr, D_2O, 6 hormones, extra plasma, elect, creat, PP, osmol, PD, Hct) , record exact time
2) Spirometry
3) Symptoms (LL, VA's, ESQ)

4) Cognitive testing
5) Check "record" button on Consentius to record following resp. file
6) Anesthetic for arterial, calibrate and set end-tidals
7) Respiratory measurements (plus end-tidal, BP, HR)
8) Arterial Blood
9) "End test" on Cons. and save Consc. file to appropriate HRV directory and rename as "3-breath" for next test
10) 3-breath N_2 test (twice) and 3-breath O_2 (once), record end-tidal cals

(7:00) 11) Venous blood (Evans, NaBr, D_2O) , record exact time
12) Void urine (9-12 interval), collect, (protein, elect, creat, osmol) and drink ad lib
13) Record body temp
14) Record weight

Remove catheter

7:00-7:15 Descend to "Albuquerque"

7:15-7:30 **Place subject on 13.5% O_2 and transport to VA Medical Center for MRI**
1) Symptoms (LL+VA) after MRI
2) Void urine and collect (volume, protein, creat, elect, osmol), record time after MRI

HYPOXIA
WOMEN AT ALTITUDE

PROCEEDINGS OF THE TENTH INTERNATIONAL HYPOXIA SYMPOSIUM AT LAKE LOUISE, CANADA, FEBRUARY 18-22, 1997.

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CHAPTER 5
WOMEN, EXERCISE, AND ACUTE MOUNTAIN SICKNESS

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Introduction

Acute mountain sickness (AMS) has been studied predominantly in men. However, due to physiological differences between genders (including, but not limited to, ovarian hormones), women may have different physiological responses to altitude than men. This may lead to a different incidence and severity of AMS in women. In this chapter we review the influence of the menstrual cycle, oral contraceptives (OCs), and exercise in women on susceptibility to AMS.

Incidence of AMS in Women and Men

Few researchers have compared the incidence and severity of AMS between women and men, and the results are contradictory. Honigman et al[26] studied 3,158 adults visiting moderate altitude (1900-2500 m) for recreation. Of 1,255 women included in that study, 28% developed AMS compared to 24% of the men ($p<0.01$). In another survey conducted at a higher altitude (~4000 m), Hackett et al[21] studied 278 unacclimatized trekkers in Nepal and noted no gender differences in AMS susceptibility. Similarly, Maggiorini et al[28] studied 466 climbers (17% women) in the Swiss Alps (2800-5000 m). The incidence of AMS symptoms between men (53%) and women (57%) was not different. However, there was a significantly higher incidence of HAPE in men (13%) than in women (<1%). Forty-nine men, but only one woman, had to be air-rescued due to pulmonary edema.

Women at Altitude

The first research at altitude on women was most likely in 1913 when Mabel Fitzgerald rode on horseback through the Colorado Rockies and analyzed alveolar gases of altitude residents.[12] Fitzgerald studied 43 residents, men and women, aged 18 to 70 years at moderate altitudes. She found that P_AO_2 and P_ACO_2 were the same in men and women and that hemoglobin concentration was not uniformly higher at

(P. 42-52)

Appendix 2

altitude in women, as it was in men. It was 55 years until the next major investigation of women at altitude. In 1969 Hannon et al[24] examined altitude acclimatization in eight women (19-21 years) who spent the summer working and living on the summit of Pikes Peak (4,300 m). These and other studies form the basis for our limited knowledge of the responses of women to acute and prolonged high altitude exposure.

Menstrual Cycle

Hormonal differences between phases of the menstrual cycle in women may cause variations in response to altitude. The normal menstrual cycle is, on average, 28 days long and consists of two major phases: follicular and luteal. In the follicular stage, ovarian follicular growth occurs, and follicle stimulating hormone (FSH) and luteinizing hormone (LH) are secreted. The developing follicle secretes estrogen in response to FSH and LH which signals the hypothalamus to reduce secretion of FSH and LH. In the luteal phase, progesterone and estrogen are secreted by the corpus luteum. Progesterone also causes swelling and secretory development of the endometrium. Approximately 26 days into the normal menstrual cycle, estrogen and progesterone concentrations decrease sharply and menstruation occurs.

Menstrual Cycle and Ventilation

Of the two phases, the luteal phase may have the most effect on adjustment to altitude because during the luteal phase of the menstrual cycle progesterone levels are markedly elevated and progesterone is a potent ventilatory stimulant. For example, when synthetic progesterone is given as a supplement to men or women ventilation is markedly increased.[39] Increased ventilation upon exposure to altitude is said to be the body's first line of defense on exposure to altitude (Fig. 1).[33,43] Thus, the increase in ventilation caused by high levels of progesterone during the luteal phase might be beneficial for high altitude acclimatization.

When women with complete hysterectomies were given either placebo, 1.25 mg estrogen, 20 mg progesterone, or both estrogen and progesterone together, ventilation was increased with progesterone and when given in combination with estrogen by 7±3% and 12±6%, respectively.[39] Given in combination, the synthetic hormones also increased the hypoxic ventilatory response (HVR) but not when given alone ($p<0.05$). Therefore, if an augmented HVR is necessary for better adjustment to altitude, then women taking OCs may have an advantage when visiting high altitude.

Menstrual Cycle and Fluid Balance

Fluid retention is associated with AMS; it appears that individuals with a strong diuretic response suffer less from AMS than individuals who lack this response (Fig. 1)[4,17,19,20,23,48] The changes in fluid regulating hormones with the normal menstrual cycle are still controversial; however, the results suggest higher levels of arginine vasopressin (AVP), plasma renin activity (PRA), and plasma aldosterone (ALD) during the luteal phase compared with the follicular phase.[5,13,29] Other researchers found no significant differences in these hormones between phases of the menstrual cycle.[10,35] It is clear, however, that if ovulation fails, there is no increase in these hormones.

Sundsfjord and Aakvaag[49] studied PRA and plasma renin substrate (PRS), as well as urinary ALD excretion (UAE), in 18 women. The women were divided into

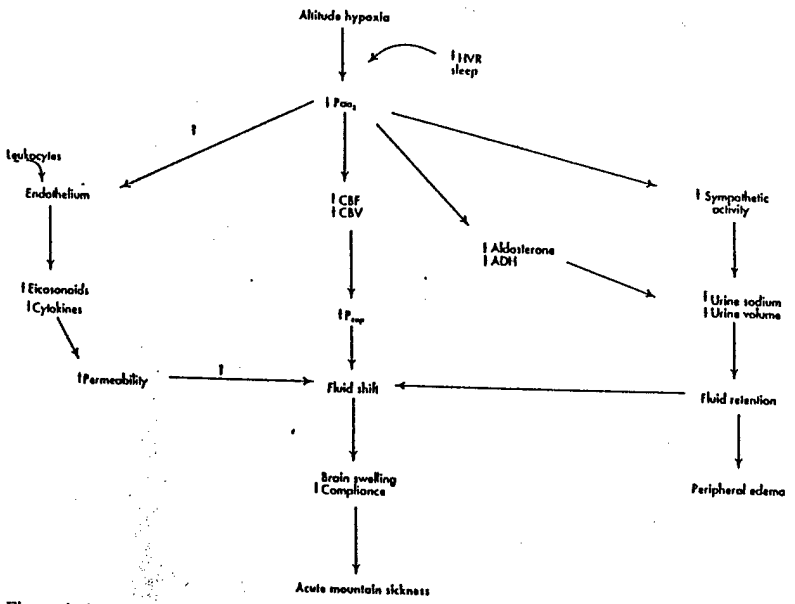

Figure 1 Proposed pathophysiology of acute mountain sickness. HVR, hypoxic ventilatory response; CBF, cerebral blood flow; CBV, cerebral blood volume; Pcap, capillary pressure; ADH, antidiuretic hormone. Reprinted from HACKETT P. H., R. C. ROACH. High-altitude medicine. In: Auerbach P. A., ed. Wilderness Medicine. St. Louis: Mosby, pp. 1-37, 1995.

either a luteal or a luteal-failure group according to their menstrual status. The luteal-failure group showed no significant difference in PRA between the first and second half of the menstrual cycle. However, the luteal group showed a significant increase in PRA during the luteal phase. No difference in PRS between menstrual cycle phases was noted for either group. The UAE rose significantly during the luteal phase in the luteal group, but did not change in the luteal-failure group.

Michelakis et al[29] measured PRA and ALD in six women throughout their menstrual cycles. Five of the 6 women had ovulatory cycles while one failed to ovulate and was considered anovulatory. In the ovulatory cycles both PRA and ALD increased during the luteal phase when progesterone levels were highest. The anovulatory subject had no change in either PRA or ALD throughout her cycle.

Forsling et al[13] studied the variation in the AVP levels throughout the menstrual cycles of eight women. AVP levels were highest at the time of ovulation and lowest at the onset of menstruation. In a later study, Forsling and colleagues[14] studied AVP levels in post-menopausal women given 2 mg/day of estradiol valeriate and/or 10 mg/day of medroxy progesterone (MPA). Estradiol treatment alone resulted in significantly increased AVP levels, while MPA treatment alone had no effect on AVP levels. However, MPA in combination with estradiol treatment resulted in a gradual decrease in AVP levels. The combination treatment most closely mimics the physiology of the luteal phase. During the luteal phase of the menstrual cycle, both

progesterone and estrogen levels are high, thus it seems likely that the combination of these two hormones results in suppression of AVP.

Unlike the studies by Forsling,[14] other researchers have reported no significant differences in AVP levels during the menstrual cycle; however, there are methodological differences that may account for the discrepancies. DeSouza and colleagues[10] found no difference in AVP throughout the cycles of 16 female runners. Eight runners were amenorrheic and eight were eumenorrheic. No difference was found in resting AVP or PRA between the two menstrual cycle phases. However, ALD was significantly greater during the luteal phase in the eumenorrheic runners. The pre-exercise estrogen and progesterone levels for both the amenorrheic and eumenorrheic groups were similar. Thus, as is often the case with physically active women, especially runners, estrogen and progesterone levels can be lower than in their less active counterparts.

Punnonen and others[36] studied AVP changes during the menstrual cycles of 14 ovulatory women. AVP was not significantly different throughout the cycle. However AVP tended to increase at the time of ovulation when estrogen was highest and to fall when progesterone was rising. The failure to find significant differences in AVP levels may be due to not measuring AVP during menstruation when AVP levels are the lowest.[13]

The effect of menstrual status (eumenorrheic versus amenorrheic) on ALD, atrial natriuretic peptide (ANP), and PRA was further studied in a group of women, aged 18 to 37 years.[10] Plasma ALD was found to be lower in the follicular phase than the luteal phase in the eumenorrheic women. In addition, ALD was higher in the eumenorrheic group versus the amenorrheic group during a submaximal exercise test. Before exercise, plasma ANP and osmolality were similar between menstrual cycle phases and between eumenorrheic and amenorrheic groups, but four minutes after exercise ANP was elevated similarly in all groups. Plasma volume changes were similar between groups and no significant relationships existed between plasma ANP or PRA. Progesterone and ALD were positively correlated during the luteal phase of the menstrual cycle. In summary, when a woman travels to altitude during her luteal phase it is unknown whether the high levels of progesterone would be of benefit due to increasing ventilation, or whether they would be detrimental by causing fluid retention and thus rendering her more susceptible to AMS.

Menstrual Cycle and Exercise Performance

Exercise performance may be affected by phase of the menstrual cycle. Schoene et al[47] examined exercise performance between menstrual cycle phases in highly trained eumenorrheic women runners, non-trained eumenorrheic women, and highly trained amenorrheic women runners, aged 17 to 37 years. They compared the effects of menstrual cycle phase in the eumenorrheic women and the effects of training status in all women. They measured the HVR, hypercapnic ventilatory response (HCVR), exercise $\dot{V}_E/\dot{V}O_2$ and $\dot{V}O_{2max}$. The eumenorrheic women had significant increases in resting ventilation and HVR during the luteal phase, with a higher HVR in the eumenorrheic athletes compared to the non-athletes. The amenorrheic group had no differences in HVR from the highly trained eumenorrheic women. The HCVR was higher in the luteal phase for the eumenorrheic athletes but not for the non-athletes. Also in the eumenorrheic women, the non-athletes had a greater exercise performance during the follicular phase versus the luteal phase, while there was no change in performance in the eumenorrheic athletes. The $\dot{V}_E/\dot{V}O_2$ was greater in the luteal phase for all eumenorrheic women during the entire exercise protocol. The mechanism of the increase in ventilation during the luteal phase is not known.

The possible relationship between increased ventilatory response and reduced exercise performance has also been examined.[6] Ten untrained men (age 27 years) were given ten milligrams medroxyprogesterone acetate (MPA) or placebo before an exercise test in a double-blind study. Each subject performed a $\dot{V}O_{2max}$ test under the influence of MPA or placebo. HCVR was unchanged, resting P_aCO_2 was reduced, and resting pH was increased with MPA administration. Exercise blood gases were similar between groups. Blood lactate increased and bicarbonate decreased more in the MPA group than the control group ($p<0.05$). There was no overall effect on cardiovascular function with MPA, and no difference between MPA and control in $\dot{V}O_2$ for a given workload. Maximal exercise performance as measured by $\dot{V}O_{2max}$, maximum workload, and perceived exertion did not change with MPA treatment. During submaximal performance, $\dot{V}_E$ increased only at 33 and 50 percent $\dot{V}O_{2max}$. When related to absolute carbon dioxide output rather than relative oxygen uptake, $\dot{V}_E$ with MPA was increased at all workloads. The authors suggested there may be a greater effect of MPA during endurance exercise and that their results were similar to studies of women in their luteal phase. However, MPA has 15 times the progestational activity of naturally occurring progesterone and may not cause the same hormonal elevation of the *in vivo* control of ventilation.

Regensteiner et al[40] used mild and moderate exercise to manipulate metabolic rate and measured HVR and HCVR. They studied 12 women (23 to 40 years) in their follicular phase and 13 men (22 to 35 years) who were recreational athletes. End tidal PCO_2 and PO_2, $\dot{V}_E$, SaO_2, heart rate and tidal volume were measured. Mild exercise consisted of leg lifts that increased resting $\dot{V}O_2$ by 25%. Moderate exercise increased $\dot{V}O_2$ to approximately four times resting and consisted of cycling at 37 Watts for women and 49 Watts for men on a cycle ergometer. Women had greater ventilatory equivalents for O_2 and CO_2 and tended to have lower end tidal PCO_2 in mild and moderate exercise. Therefore, women had greater alveolar ventilation which could not be accounted for by HVR or HCVR. Resting HVR and HCVR were similar between genders. However, during mild exercise, HVR was greater in men suggesting that they have greater sensitivity to mild changes in metabolic rate.

Oral Contraceptives

Studying women taking OCs offers an opportunity to look at responses to altitude with control over hormonal fluctuations that occur during the normal menstrual cycle. It is unknown whether OCs would make women more or less susceptible to AMS. With oral contraceptive use, the levels of progesterone and estrogen are kept at an elevated level in relation to the follicular phase, and therefore the hormonal status is similar to the luteal phase and may have the risks and benefits during altitude exposure that are associated with the luteal phase of the menstrual cycle. Oral contraceptives consist of synthetic progesterone and estrogen and are taken to prevent ovulation or to regulate menstruation. The levels of estrogen and progesterone are kept constant throughout the cycle with monophasic OCs, but the hormone levels increase progressively with biphasic and triphasic OCs. The presence of these synthetic progesterones and estrogens prevents the secretion of FSH and LH releasing factors from the hypothalamus which normally act on the pituitary

to release FSH and LH.[42] Because of the absence of these gonadotropin hormones, follicular growth and maturation, and ovulation are prevented,[42] ovarian steroid production is inhibited, and the synthetic steroids now maintain the uterus.[42] As occurs with the natural withdrawal of progesterone and estrogen in the last week of a eumenorrheic woman's menstrual cycle, the cessation of OCs in the last seven days of a 28 day cycle causes menstruation to occur.[42]

A concern when studying women who are taking OCs at altitude is that there are many types of OCs and the research comparing the potencies of different OCs is conflicting. One test of potency between OCs is the delay of menses test.[51] In this test, a set of OCs is taken every day. If breakthrough bleeding occurs before the last of the OCs are taken, the test is negative. If no bleeding occurs while the OCs are taken, the test is positive. Swyer[51] used the delay of menses test on women (< 38 years) with normal menstrual cycles taking ethinyl estradiol, a synthetic estrogen, with either norethindrone, norethindrone acetate, ethynodiol diacetate or norgestrel. They found that norgestrel was two to three times more potent then norethindrone while norethindrone was two times more potent than norethindrone acetate and ethynodiol diacetate in the delay of menses test. Dorflinger[11] reviewed several studies on potencies of different OCs and concluded that delay of menses data indicated that norethindrone, norethindrone acetate, and ethynodiol diacetate are equivalent in potency and norgestrel is five to ten times and levonorgestrel is ten to twenty times the potency of norethindrone.

The elevated progesterone levels with oral contraceptive administration may result in higher resting ventilation. The potential effects of oral contraceptive use on ventilation were studied in twelve women aged 21 to 30 years.[32] Vital capacity, tidal volume, resting $\dot{V}_E$, resting $\dot{V}O_2$, forced vital capacity in one second, midmaximal expiratory flow, and $\dot{V}O_{2max}$ were measured prior to starting OCs, and then three and six months after starting OCs. Resting tidal volume increased after oral contraceptive treatment ($p<0.01$). Resting minute ventilation increased at three months of treatment versus before and decreased from three to six months, although these changes were not significant. Exercise ventilation increased over time with use of OCs.

Oral contraceptives may also alter fluid regulating hormones which could contribute to increased or decreased susceptibility to AMS. Huisveld et al[27] studied the effects of OCs and exercise on the renin-angiotensin system in 20 highly trained athletes (10 OC and 10 non-OC) compared to 24 sedentary females (13 OC and 11 non-OC). Women on OCs had suppressed renin angiotensin activity as measured by lower pro-renin and active renin concentrations, but higher renin substrate concentrations. This suppressive effect of OCs on the renin-angiotensin system was potentiated with exercise, suggesting that OCs may provide a protection from development of AMS by preventing fluid retention. However, another study showed no significant differences in renin activity between women using OCs compared to renin activity in days seven to 12 of a normal menstrual cycle in women not using OCs.[9]

Other effects of OCs include increased resting human growth hormone levels, decreased resting blood glucose, increased free fatty acid concentration during mild exercise,[7] increased exercise human growth hormone, and increased reliance on fat and reduced carbohydrate oxidation during prolonged exercise. It is unknown whether these actions of OCs contribute to AMS.

Exercise and AMS

Rapid rate of ascent to altitude increases the severity of AMS.[22] Hackett[16] found that climbers taking less than four days to reach a 4,300 m base camp at Mt. McKinley were more likely to get ill than subjects taking five to 10 days. In this case, the rate of ascent was increased by increasing physical exertion and resulted in greater incidence of AMS. Our personal observations, along with anecdotal reports by others,[15,34,38] suggest that overexertion may be related to the development of AMS. Also, the incidence of AMS is generally lower when subjects passively ascend to high altitude (as in an altitude chamber or by helicopter ascent on mountains) compared to when they exercise to gain altitude.[37] Thus, although prior physical fitness is unrelated to AMS susceptibility,[18,25,26] exertion during ascent may increase the severity of AMS.

Exercise and Ventilation at High Altitude

It is well established that exercise at altitude decreases SaO_2.[8,46,50] West et al[55] reported that six experienced male climbers, aged 23 to 50 years, had reduced SaO_2 from rest to increasing workloads on a cycle ergometer, along with an increased alveolar-arterial oxygen difference at 5,791 m. This suggests that there are diffusion limitations in the lung resulting in a continued fall in the partial pressure of oxygen in mixed venous blood (P_vO_2) and a desaturation of arterial blood.[52,54,55] In young men (21 to 31 years) studied in Operation Everest II, whose fitness ranged from trained to untrained, the alveolar-arterial oxygen difference increased and P_aO_2 was reduced with exercise.[50] Resting and submaximal cardiac output was maintained and P_vO_2 was reduced. The reduction in P_vO_2 and increase in arteriovenous difference was linearly related to $\dot{V}O_2$. This suggests that at a given submaximal $\dot{V}O_2$ at altitude, a given level of $\dot{V}O_2$ was achieved by reducing P_vO_2 instead of increasing cardiac output.[50,53] If exercise does increase AMS symptoms, enhanced arterial oxygen desaturation and decreased P_vO_2 may be among the initiating events.

Ventilation is linked to arterial oxygen desaturation. Schoene et al[44] found a significant negative correlation between HVR and arterial oxygen desaturation at high altitude. Subjects with a brisk HVR were able to reach and sleep at higher altitudes than subjects with a low HVR. They concluded that subjects with a low HVR have a lower P_AO_2 and a higher $PaCO_2$, which shifts the oxyhemoglobin dissociation curve to the right. Under these conditions, hypoxic exercise would facilitate unloading of oxygen from hemoglobin to the tissues, and limit loading of oxygen at the lungs, resulting in decreased SaO_2.

Exercise and Fluid Balance at High Altitude

Exercise at any elevation affects fluid balance as does hypoxia without exercise. Therefore, it is important to understand the dynamics of fluid balance in humans when exercising at high altitudes.

Exercise at sea level increases AVP, PRA, and ALD secretion[1] which could cause fluid retention. During exercise over five days at low altitude, Milledge et al[31] found that five men (23 to 48 years) had increased PRA and ALD activity at the end of every day, with peak values reached on the second or third days. Increased PRA and ALD activity may have directly caused retention of sodium and caused slight leg

edema.

In 18 male mountaineers, Bärtsch et al[2] found that ALD and AVP levels were greater before and after exercise in subjects with AMS than in subjects without AMS, and suggest that the sodium and fluid-retaining effects of the ALD and AVP responses override the renal effects of ANP in AMS.[2] In another study by the same group, fluid homeostasis was examined in 15 healthy mountaineers on a controlled ascent to 4,559 m.[3] PRA, ALD, AVP, and ANP did not change at rest in subjects without AMS. Subjects with AMS had significant weight gain and increased levels of ANP. The positive correlation of ANP and the increase in cross-sectional area of the right atrium,[3] and a decrease in hematocrit suggest that the increase in ANP in AMS may be secondary to fluid retention and an increase in central blood volume.[4]

In addition, nine male soldiers who performed submaximal exercise at sea level, on acute exposure to 4,300 m (after less than two hours at altitude), and during chronic exposure (after two weeks at 4,300 m) had increased levels of ANP while exercising only on acute exposure to altitude, but not while exercising at sea level or during chronic exposure to altitude ($p<0.05$).[41] From these data it appears that the ANP response changes during acclimatization to altitude possibly because of decreases in cardiac output and stroke volume which would reduce atrial stretch and therefore inhibit ANP release. Thus, ANP may increase in subjects secondary to exercise but independent of AMS, and acclimatization to altitude may lead to a reduction in ANP levels. In summary, hypoxia-induced and/or exercise-induced increases in ALD, PRA, AVP and ANP may explain sodium and fluid retention in subjects developing AMS. Further studies are needed to determine the cause and effect relationships between hypoxia, exercise and the hormonal regulation of fluid balance at high altitudes.

Fitness and AMS

Success at altitude is difficult to predict. For example, some successful climbers have augmented HVR upon arrival at altitude while others have blunted hypoxic ventilatory responses.[45] If HVR is critical for successful climbing, then motivation or other factors may lead to the success of the latter group.[45] Sea-level $\dot{V}O_{2max}$ does not seem to predict climbing success, likely because climbing is usually a prolonged submaximal activity.[45] Some have even suggested that a high level of training may be inversely related to climbing success at very high altitudes. For example, in Operation Everest II, two of the most highly trained subjects were removed from the chamber before the end of the study, suggesting more trained subjects may be less tolerant of extreme altitude. Milledge et al[30] studied fitness and AMS in 17 men aged 23 to 55 years. No correlation was found between fitness and AMS. Thus, fitness at sea level does not predict susceptibility to AMS, and very fit individuals may perform suboptimally at very high altitudes. The limited studies on women exercising in hypoxia give no reason to suspect significant differences from men in the relationship of sea level fitness to susceptibility to AMS.

Summary

Though it is tempting to speculate about significant differences between men and women acutely exposed to high altitudes based on the influences of the ovarian hormones, data available to date support only minimal differences in physiologic responses, and essentially the same susceptibility to AMS. Further studies are currently underway to resolve the roles of gender, the menstrual cycle and oral contraceptives in physiological responses to both acute and prolonged hypoxia.

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